REMARKS

Claims 1-4, and 14-16 are pending in this patent application. Claims 7-9 were withdrawn from consideration as being directed to non-elected subject matter. None of the claims has been allowed.

At the bottom of page 2 of the Action, the Examiner rejected claims 1-6 and 10-11 Under 35 USC 112, first paragraph. The Examiner states, in part:

> Claims 1-6, 10, 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for co-administration of 25 mg 3-oxo-4-aza-7.beta.-methyl-16.beta.-(4-methylphenoxy)-5.alpha.-androst-1-ene and 5 mg 17.beta.-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5-.alpha-androst-1-en-3-one (finasteride) (Example 4 in specification), N-(2,5-bis-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5 alpha-androst-1-ene-17 beta-carboxamide (dutasteride) (Example 5 in specification), N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5 alpha-androst-1-ene 17.beta-carboxamide (Example 6 in specification), 25 mg 3-oxo-4-aza-7.beta.-methyl-16.beta.-(4-methylphenoxy)-5.alpha.-androst-1-ene (Example 7 in specification) in treating abdominal obesity does not reasonably provide enablement for all the compounds encompassed by structural formula I, III and IV (claim 1) in a method of treating visceral adiposity and metabolic syndrome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope of these claims.

The Examiner continues at the middle of page 9 and subsequently at the bottom of page 11 as follows:

> Claims 1-6, 10, 11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for co-administration of 25 mg 3-oxo-4-aza-7.beta.-methyl-16.beta.-(4-methylphenoxy)-5.alpha.-androst-1-ene and 5 mg 17.beta.-(N-tert-butylcarbamoyl)-3-oxo-4-aza-5-.alpha-androst-1-en-3-one (finasteride) (Example 4 in specification), N-(2,5-bis-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5 alpha-androst-1-ene-17 beta-carboxamide (dutasteride) (Example 5 in specification), N-(2-trifluoromethyl-phenyl)-3-oxo-4-aza-4-methyl-5 alpha-androst-1-ene 17.beta-carboxamide (Example 6 in specification), 25 mg 3-oxo-4-aza-7.beta.-methyl-16.beta.-(4-methylphenoxy)-5.alpha.-androst-1-ene (Example 7 in specification) in treating abdominal obesity and the prior art being enabling for administration of testosterone to middle-aged men and reporting the associated effects that include decreased visceral fat and glucose concentrations and increased insulin sensitivity does not reasonably provide enablement for treating metabolic syndrome with all the pro-drugs of testosterone as claimed.
>
> The specification does not teach or show any combination therapy of any of the compounds with testosterone analog or prodrugs. The

> specification does not show at what dosages of these compounds in combination with testosterone can be effective in treating the conditions claimed. The specification is not adequately enabled to show how to make prodrugs of testosterone or using prodrugs of testosterone along with the compounds claimed in Claim 1 in treating metabolic syndrome disorders.

Applicants make no admissions with regard to these rejections. Nonetheless, Applicants have amended their claims in order to advance the prosecution of the patent application. As will be seen, applicants claims are no longer directed to generic formulae I, II, III, or IV. Moreover, applicants' claims are no longer directed to testosterone analogs. Given that by definition, a testosterone prodrug "releases" testosterone, applicants have retained testosterone prodrugs. Applicants reserve the right to prosecute cancelled or unclaimed subject matter in a continuing or divisional application.

Beginning at page 14 of the Office Action, the Examiner rejects claims 1-6 and 10-11 as obvious. At page 16, the Examiner continues:

> Accordingly, it would have been obvious to one having ordinary skill in the art to use finasteride in treating metabolic syndrome because the prior art teaches that administration of finasteride increased the amount of testosterone and testosterone administration to middle-aged men is associated with decreased visceral fat and glucose concentrations and increased insulin sensitivity. One having ordinary skill in the art would have been motivated to use finasteride and add testosterone as a second agent in treating metabolic syndrome in expectation of therapeutic benefits in attaining decreased visceral adiposity, glucose concentrations and increased insulin sensitivity.

Applicants respectfully traverse. As discussed at page 5, beginning at the end of line 28, "The present invention solves the problem of <u>safely</u> elevating T levels in aging men (by) using a well tolerated, pharmacologic therapy that does not elevated DHT levels." Applicants respectfully submit that the invention is surprisingly advantageous in terms of the improved safety and is also surprising because the art teaches away from the use of the combination of the invention.

First, I direct the Examiner to the Product Information (Label) for dutasteride and for finasteride. Both show that impotence (ED) is the most common adverse reaction to the respective 5-α reductase inhibitor. See the dutasteride Product Information at page 17, Table 1; and the finasteride Product Information at page 18, Table 4. Another reference on this point is Esposito, et al., 2005, who report an increased occurrence of ED in men with the metabolic syndrome. Thus, the art teaches away from the use of a 5-α reductase inhibitor in the treatment of men who have, or are at increased risk of developing, ED, which includes men with the metabolic syndrome, and the claimed invention is unobvious.

The references discussed below further underscore the unexpected superiority of the claimed invention in terms of safety.

Applicants direct the Examiner to Marks, et al., 2006. In particular, applicants direct the Examiner to the dihydrotestosterone (DHT) information provided at Table 3, in the second section (the testosterone section). As shown, in this testosterone replacement study in men with moderately low to low testosterone, Marks et al. demonstrated that administration of testosterone resulted in a surprising and statistically significant increase relative to placebo of intraprostatic DHT.

Another reference on this point is Page, et al., 2006. Page et al. report on the effect of testosterone (T) supplementation on intraprostatic dihydrotestosterone (DHT) levels in healthy men who had undergone chemical castration with acyline. T supplementation led to a marked increase (~200%) in intraprostatic DHT levels in these men (see DHT prostate tissue data [acyline alone vs. acyline + T bars] in Figure 1).

Next, applicants direct the Examiner to Opposing Views, 2009. Read as a whole, applicants respectfully submit that:

1) There is a role for testosterone replacement therapy (TRT).

2) There is a debate as to whether there TRT is contraindicated in men with enlarged prostates.

3) A prominent feature in this debate is the question as to the level of added risk of prostate cancer attributable to the increase in intraprostatic DHT (as a result of TRT).

Applicants also direct the Examiner to Kaplan, et al., 2009 reporting a new analysis from the Prostate Cancer Prevention Trial. In particular, applicants direct the Examiner to the data in Figure 1 and the first paragraph in the Discussion, which supports the role of DHT (see below regarding the role of finasteride in suppress markedly DHT) as a risk factor for clinically significant prostate cancer.

Applicants also direct the Examiner to Laukkanen, et al., Oct. 2004. As shown, even before/without TRT, men with metabolic syndrome are at risk for prostate cancer.
Applicants also direct the Examiner to Geller, 1990; and McConnell, et. al., 1992. As shown, treatment with finasteride led to a marked suppression of intraprostatic DHT levels.

Given that it is now known that ED is associated with the metabolic syndrome and that men with metabolic syndrome are at increased risk for prostate cancer; and given that we now know that intraprostatic DHT is raised in men receiving TRT; and given that we know further that some risk of clinically-significant prostate cancer is attributable to DHT; and finally given that administration of finasteride reduces intraprostatic DHT, it must be recognized that the claimed invention provides a surprisingly safe and superior alternative to TRT.

Having addressed all of the outstanding objections and rejections applicants respectfully submit that the application is in condition for allowance and passage thereto is earnestly requested. The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of this application.

Respectfully submitted,

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